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EXAMINER	
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ART UNIT	PAPER NUMBER
1804	12

DATE MAILED: 10/19/95

Please find below a communication from the EXAMINER in charge of this application

In response to applicants telephone inquiry of 10-13-95, regarding the last office action taken on application 08/225,478, the following materials are supplied:

A copy of the Mitani reference is enclosed.

A PTOL-892 is supplied.

THE PERIOD OF RESPONSE TO SAID OFFICE ACTION IS THREE MONTHS AND ZERO DAYS AND IS RESTARTED TO BEGIN WITH THE DATE OF THIS LETTER.

Any inquiry concerning this communication from the examiner should be directed to Andrew Milne, whose telephone number is (703) 308-4213. The examiner can normally be reached from 7:00 to 4:00 (Eastern Standard Time) Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached at (703) 308-3153. The fax number for art unit 1804 is (703) 308-4312.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Andrew Milne
10-13-95
AM

JACQUELINE M. STONE
SUPERVISORY PATENT EXAMINER
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Claims 1-26 are currently pending in U.S. Patent Application # 08/225,478.

The disclosure is objected to because of the following informalities: multiple spelling errors exist, see: Claim 16 "thereapeutic", page 5 Ppr80 versus pPr80, page 24, line 1 should be PBMC not "PBM". Appropriate correction is required.

Applicants claim a method of transducing and reinfusing hematopoietic stem cells into a patient suffering from adenosine deaminase deficiency. Applicants' working examples cite the feasibility of this procedure and the immediate therapeutic benefits obtained from the patients involved. However, the field of gene therapy has a recognized amount of unpredictability. Applicants focused on transducing $CD34^+$ cells due to their extensive proliferative capacity to yield large numbers of transduced mature hematopoietic stem cells, theoretically for the life of the patient. Although applicants document the increase in numbers of T lymphocytes and the decrease in deoxyadenosine metabolites by the infant patients, one of ordinary skill in the art would not be able to predict these results as being sustained far into the future with any expectation of success.

Furthermore, applicants fail to demonstrate that the amount of ADA secreted by the cells would be therapeutically effective to treat SCID. Applicants disclose percentages of colonies that

had had the neo gene inserted; however, applicants do not teach high transfection of hematopoietic stem cell precursors.

Furthermore, applicants disclose the use of at least one nucleic acid sequence contained in at least one expression vehicle. Given the current level of unpredictability in the art of gene therapy, one of ordinary skill cannot predict the efficacy of a transduced cell that is reinfused into a human, with respect to its survival time and interactions with other components of the immune system. There are multiple parameters that need to be confronted when considering the chance of survival of a cell that has been transduced, ex vivo, to express an exogenous gene, and reinfused.

Applicants disclose the culturing of transduced $CD34^+$ cells in the presence of growth factors: IL-3, IL-6 and c-kit ligand. This presents further uncertainty as to whether the cells will expand in culture in the desired scenario. This is because the use of growth factors in the art is still experimental and more detailed understanding of growth factors is needed in the art Kohn further supports this viewpoint on page 1070, Exp. Hematol., "Greater understanding of the complex and interactive roles of the multiple positive- and negative-acting HGFs will play an important role in applying gene transfer into hematopoietic stem cells for therapeutic purposes."

Claims 1-26 rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-26 are vague and seemingly inconsistent in that no relationship exists between the cells that applicant intends on administering to said patient and the cord blood from where the CD34+ cells were first obtained; therefore, applicant should consider terms such as: autologous or allogenic, etc.. .

Claims 1-26 are vague in that no mention of whether the therapeutic strategy is to be *in vivo* or *in vitro* is mentioned.

Claim 1 is indefinite since it is not clear whether the "administering" is to the patient or to the "said patient CD34+ cells obtained from cord blood". Further, the term "genetically engineered" does not disclose what was done with any specificity in terms of steps of methods of said "genetic engineering". Further, there are no metes and bounds to the term "at least one" and it is indefinite what the upper bounds of "at least one" are.

Claim 1 is further indefinite because it claims a method without disclosing any therapeutic effect, and further, what would be the end point of any therapeutic effect.

Claims 1-5 and 16-26 use the phrase "at least one nucleic acid sequence encoding a therapeutic agent". Applicant fails to limit the scope of the claims to a desired amount of nucleic acid sequences, thereby making the designation "at least one" vague and indefinite.

In claim 5, the "about" is indefinite with regard to the fact that as defined, "about" has no meaning (Webster's definition: "about" -approximately, almost, in any direction, in the area, all around, etc..) with regard to how may less than or more than $5x10^{5}$/kg and 10^{7}/kg are included or excluded.

Claims 6 and 11 are also indefinite since no resulting effect upon SCID is indicated.

Claim 16 further lacks a therapeutic agent. Further, it is unclear what the result of the process will be - (i.e. what does the process produce; it is not apparently stated in the claim- What does the process make the cells do?).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

> skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Anderson(Science) taken with Moritz, and further in view of Kohn.

Applicants claim a method of administering to a patient hematopoietic stem cells of the $CD34^+$ lineage which have been genetically engineered to express the gene encoding adenosine deaminase. Anderson(Science) discusses the concerns of transducing only mature cells and not stem cells ($CD34^+$ stem cells) in the existing protocol, page 811. Anderson(Science) implies that the ability of progenitor cells to continuously express a gene that has been integrated into their genome would be beneficial for the purpose of expressing adenosine deaminase. Anderson(Science) teaches the prior art disclosing the manipulation of $CD34^+$ cells and addresses the method of transducing $CD34^+$ cells for the purpose of gene therapy with respect to hematopoietic stem cells such as the $CD34^+$ lineage. Anderson et al differ from the claims in that the reference fails to disclose the use of cord blood. However, the secondary reference Moritz et al cures the deficiency.

Moritz et al disclose the manipulation of human cord blood due to its large fraction of primitive progenitor cells. It would have been obvious to one of ordinary skill to substitute the cord blood $CD34^+$ stem cells for the stem cells of Anderson since Anderson suggests the use of $CD34^+$ stem cells and Moritz teaches that cord blood contains primitive progenitor cells capable of being transformed. Therefore, both claims 11-20 and 25 and 26 are rejected under 35 U.S.C. 103 as being unpatentable over Anderson taken with Moritz. Claims 1-10, 21-24 were rejected for reasons stated above.

Anderson and Moritz provide the motivation to combine the references. Accordingly, the modification of the method of Anderson by substituting cord blood progenitor cells as suggested by Moritz in order to obtain a method for providing a therapeutic effect was within the skill in the art at the time the claimed invention was made. From the teachings in the references, one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention; therefore, the invention as a whole is prima facia obvious, as evidence by the references, especially in absence of evidence to the contrary.

Kohn discloses the increases in percentages of successfully transduced $CD34^+$ cells while said cells are cultured with the use of hematopoietic growth factors, more specifically in the presence of IL-3, IL-6 and a c-kit ligand. Kohn was able to

prove the benefits with respect to successful transduction percentages, when culturing $CD34^+$ progenitor cells in the presence of IL-3, IL-6 and MGF.

It is therefore concluded that one of ordinary skill in the art at the time that the invention was made would have been motivated to utilize the ex vivo transduction procedure, as seen in Anderson, for the purpose of successful transduction and reinfusion of human cells, utilize $CD34^+$ cells as hematopoietic stem cells in hopes of yielding high numbers of transduced cells that have a substantial ability to proliferate and obtain said stem cells from human cord blood, as seen in Moritz, and to culture said cells in the presence of IL-3, IL-6 and c-kit ligand to promote successful transduction efficiencies, as seen by Kohn. This procedure would be able to produce cells with large proliferative capacities that are able to express an inserted gene for the life of the patient.

Claims 1-10, 21-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Anderson(Science) taken with Mitani and Culver.

Anderson(Science) et al disclose ADA gene therapy as a process in which a patient undergoes leukophoresis for the purpose of obtaining mononuclear cells, growing the cells in culture and transducing the T lymphocytes with a retroviral vector containing the normal ADA gene (as well as the NeoR gene) , and finally reinfusing the cells into said patient with the

intent that the newly inserted gene will express adenosine deaminase *in vivo*.

Mitani et al discloses the common concern of transducing only mature T lymphocytes as well. More specifically, Mitani discloses the selection of $CD34^+$ cells and subsequent transduction with a retroviral vector to insert the gene for ADA for a therapeutic purpose. Mitani closes by stating that a viral supernatant protocol is applicable to a clinical trial in ADA deficient patients, page 81, column 2.

Further, applicant's claims 5,9,14 and 21-26 disclose the expansion of cells to the amounts between $5x10^5$ to $10x10^7$ prior to administration. Culver et al (Immunol.) teaches reinfusion of lymphocytes that have been genetically altered to treat ADA deficiency. Culver teaches an average infusion amount of $1.13x10^{10}$ per patient per infusion which is higher than applicants claims in terms of infusion quantity; however, one of ordinary skill in the art at the time the invention was made would have been motivated to infuse cells genetically altered to express adenosine deaminase at a concentration that had been deemed acceptable for *in vivo* treatment or infusion a of smaller quantity thereof for the purpose of treating an infant who would have less body weight and should therefore receive less cells.

The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in

the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,2,8,9,10,13 and 14 of U.S. Patent No. 5,399,346. Although the conflicting claims are not identical, they are not patentably distinct from each other because the segment of DNA that applicant utilizes to encode the enzyme adenosine deaminase, is encompassed by claim 1 of said patent in understanding that ADA is a therapeutic protein encoded for by a particular DNA segment and that this segment is to be inserted into human blood cells. Moreover, the gene encoding adenosine deaminase is to be inserted into cells by a viral vector, and more specifically, a retroviral vector.

Any inquiry concerning this communication from the examiner should be directed to Andrew Milne, whose telephone number is

(703) 305-7519. The examiner can normally be reached from 7:00 to 4:00 (Eastern Standard Time) Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached at (703) 308-3153. The fax number for art unit 1804 is (703) 308-4312.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

AKM

Andrew K. Milne

June 31, 1995

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800